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Supreme Court of the United States

TEVA PHARMACEUTICALS USA, INC.,
ZENITH GOLDLINE PHARMACEUTICALS
(now known as IVAX PHARMACEUTICALS, INC.),
and DR. REDDY'S LABORATORIES, LTD.,
Petitioners,

v.

ELI LILLY AND COMPANY
and LILLY INDUSTRIES LIMITED,
Respondents.

On Petitions for Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

RESPONDENTS' BRIEF IN OPPOSITION TO PETITIONS FOR WRIT OF CERTIORARI

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Rule 29.6 of the rules of this Court, Respondents Eli Lilly and Company and Lilly Industries Limited state that no parent corporation or any publicly held company owns 10 percent or more of the corporations' stock.

TABLE OF CONTENTS

Page

CORPORATE DISCLOSURE STATEMENT i

I. PRELIMINARY STATEMENT.....1

II. FACTUAL BACKGROUND 2

A. The Long Search for a Safe Atypical Antipsychotic Drug 2

1. Failure of Others to Discover a Safe Atypical Antipsychotic Drug 2

2. Lilly's Initial Failures.....4

3. Success of Olanzapine.....6

III. ARGUMENT 8

A. The Facts of This Case Prove the Nonobviousness of Olanzapine.....8

1. The Prior Art Taught Away 8

2. There Was No Reasonable Expectation of Success.....9

3. Strong Evidence of Unexpected Results Demonstrates Nonobviousness 11

4. Other Secondary Indicia Including a Long-Felt but Unsolved Need and Repeated Failure of Others Show Nonobviousness 12

B. The Federal Circuit Did Not Impose Rigid TSM Requirements That Are Inconsistent with *KSR* 13

1. The Finding That It Would Not Have Been Obvious to Select Compound '222 as a "Lead" Compound Is Consistent with *KSR* 14

2. It Would Not Have Been Obvious to Modify Compound '222 to Make Olanzapine 19

3. The Federal Circuit Did Not Impose Requirements That Only "Preferred" Compounds or That Only "Preferred" Modifications Can Be Considered 22

4. Olanzapine Was Held to Be Nonobvious Because the Facts Contradicted the Petitioners' Theories 25

C. DRL Ignores Most of the Evidence and the District Court's Undisputed Findings of Fact 26

D. GVR Is Unnecessary and Would Be a Futile Exercise.....28

IV. CONCLUSION.....29

TABLE OF AUTHORITIES

FEDERAL CASES

Page

In re Baird,
16 F.3d 380 (Fed. Cir. 1994).....6, 23

Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.,
320 F.3d 1339 (Fed. Cir. 2003).....9, 10

CFMT, Inc. v. Yieldup International Corp.,
349 F.3d 1333 (Fed. Cir. 2003).....6

Graham v. John Deere Co. of Kansas City,
383 U.S. 1 (1966).....1, 8

Graver Tank & Manufacturing Co. v. Linde Air Products Co.,
336 U.S. 271 (1949) *aff'd on reh'g*.....28

KSR International Co. v. Teleflex Inc.,
No. 04-1350, 127 S. Ct. 1727 (2007).....passim

In re Kaplan,
789 F.2d 1574 (Fed. Cir. 1986).....6

Lawrence v. Chater,
516 U.S. 163 (1996).....29

In re Papesch,
315 F.2d 381 (C.C.P.A. 1963).....19

FEDERAL CASES (cont.)

In re Soni,
54 F.3d 746 (Fed. Cir. 1995).....19

Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.,
No 06-1329, 2007 WL 1839698
(Fed. Cir. June 28, 2007).....16, 17, 29

United States v. Adams,
383 U.S. 39 (1966).....1, 9, 12, 22

WMS Gaming Inc. v. International Game Technology,
184 F.3d 1339 (Fed. Cir. 1999).....8

Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal, Inc.,
231 F.3d 1339 (Fed. Cir. 2000).....16

FEDERAL STATUTES

35 U.S.C. § 103.....8, 24

35 U.S.C. § 282.....29

I. PRELIMINARY STATEMENT

The defendants in the case below were Teva Pharmaceuticals USA, Inc. and Zenith Goldline Pharmaceuticals (collectively "Teva") and Dr. Reddy's Laboratories, Ltd. ("DRL"). Teva filed a petition for a writ of certiorari on June 11, 2007, and DRL filed a separate petition for a writ of certiorari on June 28, 2007. This brief responds to arguments in both petitions.

Petitioners contend that when the Federal Circuit affirmed the district court's finding of nonobviousness, the Federal Circuit imposed rigid threshold requirements that are inconsistent with *KSR International Co. v. Teleflex Inc.*, No. 04-1350, 127 S. Ct. 1727 (2007). In fact, the Federal Circuit did not impose any such rigid requirements at all. Instead, the Federal Circuit applied well-settled legal principles to the unique evidence and facts of this case, performed a full and proper obviousness analysis under *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), and reached decisions fully consistent with *KSR*.

The technology in this case is unlike the simple mechanical combination in *KSR*, but instead resembles the unpredictable subject matter in *United States v. Adams*, 383 U.S. 39 (1966), cited with favor in *KSR*. The *Adams* court ruled that the invention at issue was nonobvious because the prior art taught away from the claimed invention, 383 U.S. at 51-52; *KSR*, 127 S. Ct. at 1740, and because there was evidence of secondary indicia of nonobviousness, such as unexpected results. 383 U.S. at 43, 52; *KSR*, 127 S. Ct. at 1740. Similarly, olanzapine was found to be nonobvious in this case because the prior art taught away from modifying prior art compounds to obtain olanzapine, the effects of modifications of compounds in the class that included

olanzapine were highly unpredictable, and there was substantial evidence of unexpected results and other secondary indicia of nonobviousness, including a long-felt but unsolved need and failure of others to solve the problem. Reevaluation in light of *KSR* would not change the results of this case.

II. FACTUAL BACKGROUND

A. The Long Search for a Safe Atypical Antipsychotic Drug

1. Failure of Others to Discover a Safe Atypical Antipsychotic Drug

Schizophrenia was largely untreatable before the discovery in the 1950s of "typical" antipsychotic drugs. App. 31a-32a ¶¶ 15-17.[1] Those drugs, however, had distressing side effects, including crippling movement disorders. App. 32a-33a ¶¶ 17-18. In the early 1970s, hopes were raised by the discovery of an "atypical" antipsychotic drug called "clozapine" that did not cause those side effects. App. 33a ¶ 19. These hopes, however, were dashed following the discovery in 1975 that clozapine caused an often fatal blood disorder. App. 33a ¶ 20.

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[1] "Teva Pet." refers to the petition for a writ of certiorari filed by Teva and "DRL Pet." refers to the petition filed by DRL. Because the pagination is identical in the appendices of the Teva and DRL petitions, citations to "App." refers to either appendix. "CA App." refers to the joint appendix at the U.S. Court of Appeals for the Federal Circuit.

Beginning in about 1975, Lilly and many others around the world began to search for a safe clozapine-like antipsychotic drug. App. 34a-40a ¶¶ 21-42, 65a ¶¶ 125-127. The trial evidence revealed a recurring pattern of failure. *Id.* New classes of putative antipsychotic drugs were identified in the scientific and patent literature, only to be followed by reports that the most promising compounds from those classes had failed because of toxicity or lack of atypical antipsychotic efficacy. App. 65a ¶ 127, 82a ¶ 178. These pervasive failures were documented by a 1990 report in the New England Journal of Medicine stating that "[d]espite the extensive development effort in this area [reported to have involved testing about 2,000 compounds], no alternative to clozapine has been identified that has clinical antipsychotic efficacy and no extrapyramidal neurological side effects [movement disorders], but has a low risk of inducing other important toxic effects . . . ." App. 34a ¶ 23.

Many reasons contributed to these failures. The cause of schizophrenia was unknown. Clozapine was known to interact with many receptors in the brain, and it was unknown which combination of these actions was responsible for clozapine's "atypical" profile. App. 82a ¶ 178. This class of compounds was highly unpredictable—small structural changes in clozapine-like drug candidates had dramatic effects on the properties of the compounds. App. 65a-66a ¶ 127, 82a ¶ 178. Even more troubling, the cause of clozapine's toxic side effect was unknown. *Id.* The harmful side effects that doomed proposed new antipsychotic drugs were diverse and unpredictable. App. 65a-66a ¶ 127. Those working in the field were reduced to an empirical "trial and error" approach, in which both the safety and atypical antipsychotic efficacy of drug candidates could be confirmed only by testing in schizophrenic patients. App. 41a ¶ 46, 83a ¶ 181.

Certain principles guided scientists in their searches for improved antipsychotic drugs. In particular, both clozapine and the typical antipsychotics had certain chemical groups (so-called "neuroleptic substituents") attached to their chemical backbones that were believed to be necessary for their antipsychotic activity. App. 6a, 34a-35a ¶ 24, 40a ¶ 44, 83a ¶ 179. The most common of these so-called "neuroleptic substituents" were halogen atoms, such as chlorine and fluorine. *Id.* Removal of the halogen substituent from clozapine and from other proposed antipsychotics destroyed their efficacy. App. 65a-66a ¶ 127. Virtually every proposed new antipsychotic drug had a neuroleptic substituent, usually a halogen, and the district court found as a fact that the prior art *taught away* from attempting to make a new antipsychotic drug that lacked a neuroleptic substituent. App. 14a, 16a, 81a ¶ 176, 221a ¶ 61.

2. Lilly's Initial Failures

In the late 1970s and early 1980s, Lilly's experience of failures paralleled that of others skilled in the art, including researchers in industry and academia. Indeed, the early Lilly patents and publications in this area ultimately became testaments to Lilly's failed attempts to solve the problem. A promising class ("genus") of millions of compounds was discovered, and a patent application was filed in 1975, which issued as U.S. Patent No. 4,115,574 ("the '574 patent"). App. 35a ¶ 26. The '574 patent described those millions of compounds, as others had described their own classes of compounds, as useful in the treatment of certain psychotic conditions. The petitioners apparently refer to statements made in 1975 in the '574 patent application about that whole genus of compounds as a basis for contending that, in 1990 when the olanzapine patent application was filed, compound '222 was believed to be

effective.[2] Teva Pet. at 4, DRL Pet. at 16. However, as was the case for early reports of others in the industry, Lilly's lead compounds described in the '574 patent failed. App. 36a-38a ¶¶ 31-38. As an expert for one of the petitioners admitted, by 1990 nobody believed the naively optimistic 1970s-vintage reports of class-wide antipsychotic activity. CA App. A26571.

Like others skilled in the art, Lilly concentrated its efforts on compounds with a halogen neuroleptic substituent. App. 36a ¶ 29. The '574 patent focused particularly on a halogenated compound here called "ethyl flumezapine," App. 66a-67a ¶¶ 130-131, which was Lilly's lead development candidate in the fall of 1975. App. 36a ¶¶ 31-32. Ethyl flumezapine was abandoned when toxicology tests in dogs revealed widespread blood problems reminiscent of the fatal disorders seen with clozapine in humans. App. 37a ¶ 33.

In an effort to find a compound free of that problem, Lilly next spent four years trying to develop a closely related compound now called "flumezapine," which also bore a halogen substituent. App. 37a-38a ¶¶ 34-36. Flumezapine did not cause the blood problems in animals seen with ethyl flumezapine. App. 37a ¶ 35. Notwithstanding success in animal tests, flumezapine failed when clinical trials revealed problems in liver and muscle enzymes in the treated patients, App. 38a ¶ 36, which caused both the FDA and British regulatory authorities to halt the clinical trials. App. 38a ¶¶ 37-38.

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[2] Petitioners refer to this prior art compound, which Lilly and the court decisions call "compound '222," as "ethyl olanzapine."

3. Success of Olanzapine

In a last-ditch effort to find a safe atypical antipsychotic drug, Lilly decided to study olanzapine as a potential drug candidate, first through years of rigorous animal studies, and then through cautious clinical administration to humans. Olanzapine is not described in the '574 patent, although it falls within the large genus of compounds defined in that patent.[3] It was an unusual choice because it lacked a halogen or other neuroleptic substituent that was believed to be essential for antipsychotic activity, and many at Lilly thought that olanzapine would not work and should not be pursued for that reason. App. 40a ¶ 44. The development of olanzapine was long and difficult because of fears that it might also have undesirable side effects, App. 40a-41a ¶¶ 45-46, 146a-148a ¶¶ 364-365, 368-370, but it was ultimately proven not to have the side effects that had forced clozapine and flumezapine out of the clinic. App. 41a ¶ 47. Olanzapine ultimately reached the market in 1996 and became a successful antipsychotic drug.

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[3] Olanzapine is thus a "selection invention." Species falling within a broad prior art disclosure are regularly found to be patentable where the species would not have been obvious from the generic disclosure. *E.g.*, *In re Kaplan*, 789 F.2d 1574, 1578, 1580 (Fed. Cir. 1986) (prior generic patent claim did not render later selected species claim unpatentable for double patenting); *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994) (prior generic disclosure did not render later selected species obvious under 35 U.S.C. § 103); *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1340 (Fed. Cir. 2003) ("[i]mprovement and selection inventions are ubiquitous in patent law. . ."); App. 204a ¶ 14.

App. 87a-88a ¶¶ 192-94. Olanzapine has the desirable atypical properties of clozapine but does not cause the fatal blood disorder seen with clozapine. App. 41a ¶ 47.

Based on the results of the initial clinical trials, a patent application claiming olanzapine and its use for treating schizophrenia was filed in 1990, more than 16 years after Lilly began its search for a safe atypical antipsychotic drug. App. 43a ¶¶ 53-54. Lilly's patent attorneys correctly anticipated that, based upon a then-prevailing practice at the PTO, the patent examiner would initially reject olanzapine as obvious and require a comparison between olanzapine and compound '222, the structurally closest prior art compound within the genus disclosed in the '574 patent. Therefore, Lilly performed a long-term toxicology study in dogs to determine whether there was a difference in the toxicity profile between olanzapine and compound '222. App. 42a ¶¶ 49-50. The study revealed an entirely unexpected result—the prior art '222 compound caused a large, statistically significant elevation in blood cholesterol levels in female dogs while olanzapine did not. App. 42a ¶ 51, App. 91a ¶ 204, 93a ¶ 209. This unexpected benefit of olanzapine over compound '222 played a role in establishing the nonobviousness of olanzapine in both the Patent and Trademark Office (PTO) and the district court litigation. App. 43a ¶ 52, *discussed in detail* 89a-129a ¶¶ 199-302.

III. ARGUMENT

A. The Facts of This Case Prove the Nonobviousness of Olanzapine

Before addressing the nonexistent legal errors alleged by petitioners, it is worth reviewing the wealth of factual evidence that, under well-settled legal principles, mandates a finding that olanzapine would not have been obvious from the prior art compound '222. Nonobviousness under 35 U.S.C. § 103 is a legal conclusion that is based on basic factual inquiries. *Graham*, 383 U.S. at 17-18; *WMS Gaming Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355 (Fed. Cir. 1999) (citing *Graham*). At trial, twenty-three thousand pages of documentary evidence were woven together by the testimony of 40 witnesses that informed the trial court's extensive Findings of Fact, which the petitioners never challenged on appeal as clearly erroneous and do not challenge here.

After analyzing the state of the art reflected in this evidentiary record, and after considering each of the *Graham* factors, the district court found that olanzapine would not have been obvious in view of compound '222, and the Federal Circuit affirmed. That decision is firmly grounded in numerous unchallenged Findings of Fact in the district court's meticulously reasoned opinion.

1. The Prior Art Taught Away

Based upon extensive evidence, the district court found that the prior art *taught away* from modifying non-halogenated compound '222 by replacing the ethyl substituent with a methyl substituent to make olanzapine. App. 14a, 16a, 40a ¶ 44, 221a ¶ 61. Instead, the art taught

that antipsychotic drugs, to be effective, required a "neuroleptic substituent" such as a halogen (e.g., a chlorine or a fluorine), which both compound '222 and olanzapine lack. App. 14a, 16a, 34a-35a ¶ 24, 40a ¶ 44, 79a ¶ 170, 83a ¶ 179. Because compound '222 lacked a neuroleptic substituent, a person of ordinary skill would not even have selected it as a compound to modify in order to make an atypical antipsychotic drug. App. 220a-222a ¶¶ 60-62 (*citing* 73a-78a ¶¶ 154-169). However, even if that person of ordinary skill had selected compound '222 as a starting point, then it would not have been obvious to modify it to make olanzapine. App. 222a-223a ¶¶ 63-64 (citing 79a-80a ¶¶ 170-173). "The prior art would have instead suggested modification by adding a halogen atom to supply the neuroleptic substituent as a trigger for antipsychotic activity." App. 15a; *see also* 79a ¶ 170. Prior art teaching away from the claimed invention is a factor strongly supporting nonobviousness. *Adams*, 383 U.S. at 52; *KSR*, 127 S. Ct. at 1740.

2. There Was No Reasonable Expectation of Success

KSR recognized the significance of predictability in determining whether an invention would have been obvious. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 127 S. Ct. at 1739. A necessary corollary is that when results of modifying the prior art are unpredictable, the modification is likely to be nonobvious. *KSR* is fully consistent with the well-established principle of patent law that for a proposed modification of the prior art to have been obvious, there must have been a reasonable expectation of success, i.e. that the modification would achieve the intended result. *Boehringer*

Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir. 2003).

Here, the evidence established that modifications of molecules in the class of potential antipsychotic drugs yielded results that were highly *unpredictable*. Even very small changes in structure resulted in drastic changes in efficacy or toxicity. App. 65a-66a ¶ 127. The prior art's teaching away from compounds without neuroleptic substituents, combined with the unpredictability of modifications to molecules in this genus of compounds, led the trial court to find as an unchallenged fact that there was *no reasonable expectation of success*; that is, that there was no reasonable expectation that petitioners' proposed modification of compound '222 to make olanzapine would have succeeded as a safe and effective atypical antipsychotic. App. 14a-15a, 82a-84a ¶¶ 178-182. *KSR* has not altered the requirement that a reasonable expectation of success is necessary for obviousness, and petitioner's arguments do not overcome that hurdle.

"When there is a design need or market pressure to solve a problem and there are a finite number of identified, *predictable* solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1742 (emphasis added). Petitioners repeatedly quote that statement to argue their theory that it would have been obvious to modify compound '222 to make olanzapine. Teva Pet. at 12-16; DRL Pet. at 17. However, starting with compound '222 and replacing its ethyl group was not an "identified solution," *see* § III.B *infra*, and the results of that modification were unpredictable. Indeed, a person of ordinary skill would have predicted failure of a compound that lacked a neuroleptic substituent, not success.

3. Strong Evidence of Unexpected Results Demonstrates Nonobviousness

Unlike *KSR*, the district court and the Federal Circuit found strong evidence of *unexpected results* that supports the patentability of olanzapine over compound '222. App. 15a, 19a, 89a-122a ¶¶ 199-274. In an animal toxicology test of the type regularly used to detect potential for toxicity in humans, the prior art compound '222 caused a marked increase in cholesterol in female dogs treated with that compound, while there was no elevation of cholesterol in dogs treated with olanzapine. App. 73a ¶ 153, 93a-94a ¶¶ 209, 211, 120a-121a ¶ 271. The effect of compound '222 in raising cholesterol was entirely unexpected, and therefore the absence of that undesirable side effect by the structurally similar olanzapine was an unexpected benefit of the invention compared to the prior art. The experiments supporting this finding were intensively scrutinized during the trial, and the validity of the results was confirmed. App. 89a-122a ¶¶ 199-274, *see* 43a ¶ 52. It is particularly noteworthy that a sophisticated dog study sponsored by one of the petitioners, using much larger groups of experimental animals, fully replicated and confirmed the results of Lilly's dog study. App. 91a-94a ¶¶ 205-211, 112a-113a ¶ 254.

The elevation of cholesterol seen in dogs treated with compound '222 was large, statistically significant, and biologically important, thus demonstrating a substantial benefit of olanzapine over prior art compound '222. App. 93a ¶ 209, 120a-122a ¶¶ 270-274, 126a-127a ¶ 295. This evidence showed that whatever effect olanzapine might have on cholesterol in humans, compound '222 would be worse. *See* App. 121a-122a ¶¶ 272-73. Nothing in *KSR* diminishes

the probative value of these unexpected results in establishing the nonobviousness of olanzapine.

4. Other Secondary Indicia Including a Long-Felt but Unsolved Need and Repeated Failure of Others Show Nonobviousness

In addition to unexpected results, the district court and the Federal Circuit found that there was substantial evidence of other *secondary indicia of nonobviousness* to fully rebut any assertion of obviousness based simply on structural similarity. App. 18a-19a, 86a-87a ¶¶ 185-191, 88a-122a ¶¶ 197-274. Extensive evidence proved that there was a *long-felt but unsolved need* for a safe atypical antipsychotic drug. App. 19a, 86a-87a ¶¶ 185-190. The *repeated failure of others* is well documented in the record. App. 5a-6a, 19a, 34a ¶¶ 21-23, 87a ¶ 191, 227a ¶ 76. The success of olanzapine was also met with *acclaim in the industry*, as would be expected of an important nonobvious innovation. App. 19a, 88a ¶ 197.

When considering petitioners' contentions regarding alleged inconsistencies with *KSR*, it is important to keep in mind that the holding below of nonobviousness of olanzapine over compound '222 is grounded on uncontested factual findings that the art taught away from the claimed invention, that there was no reasonable expectation of success based on the unpredictability of the compounds, and that there was strong evidence of unexpected results and other indicia such as a long-felt but unsolved need and the failure of others. All of these are recognized as important indicia of nonobviousness. *Adams*, 383 U.S. at 43, 52; *KSR*,

127 S. Ct. at 1740. They are also important distinctions between this case and *KSR*.

B. The Federal Circuit Did Not Impose Rigid TSM Requirements That Are Inconsistent with *KSR*

KSR rejected applying the teaching-suggestion-motivation ("TSM") test as a rigid rule. Nevertheless, it recognized that the TSM test was a "helpful insight" for considering obviousness and that the Federal Circuit has "no doubt applied the [TSM] test in accord with" *Graham* and the principles stated in *KSR* and in many cases. 127 S. Ct. at 1741. "There is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* Error was found in *KSR* only "when a court transforms the general [TSM] principle into a rigid rule that limits the obviousness inquiry." *Id.* Indeed, *KSR* acknowledged that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* at 1741.

By pointing to each example where the Federal Circuit used the word "motivation" in its opinion in this case, petitioners attempt to portray the Federal Circuit's opinion as imposing improper rigid rules that misapply the TSM test to limit the obviousness inquiry. But a fair reading of the opinion shows that the Federal Circuit imposed no rigid rules at all. Not only were there no rigid TSM tests, but each of the arguments that petitioners say should have been considered actually was considered by the courts below, and each was rejected for sound reasons.

Petitioners would analyze obviousness in a vacuum, plucking compound '222 from its obscure and unpromising position in the prior art and substituting a methyl substituent for its ethyl substituent because compound '222 is now recognized to be structurally similar to olanzapine. Teva Pet. at 6-7, 13-14; DRL Pet. at 3-4, 15-18. The rationale for this approach lies entirely in impermissible hindsight. It is only knowledge that olanzapine met the long-felt need for a safe atypical antipsychotic drug that would provide a reason to choose its adjacent homolog, compound '222, as a starting point or lead compound. This Court warned in *KSR* against "the distortion caused by hindsight bias" and to "be cautious of arguments reliant upon *ex post* reasoning." 127 S. Ct. at 1742. In the obviousness analysis, subsequent knowledge of the invention of olanzapine cannot be allowed to focus attention on compound '222. Instead, it is the teachings of the prior art as a whole, properly viewed from the perspective of a person skilled in the art *before the invention was made*, that must fairly focus attention on compound '222. As reflected in the trial court's numerous unchallenged factual findings, this the prior art did not do.

1. The Finding That It Would Not Have Been Obvious to Select Compound '222 as a "Lead" Compound Is Consistent with *KSR*

According to the petitioners, the Federal Circuit held "that Petitioners were required to demonstrate, as a threshold matter, that one of ordinary skill would have been 'motivated' to select ethyl olanzapine [i.e., compound '222] from among all the prior art compounds as a 'lead compound,'" Teva Pet. at 6, and that if a compound is not a "lead" compound it cannot be considered in the obviousness

analysis. Teva Pet. at 13-14, DRL Pet. at 9, 12-13, 15. Petitioners argue that the Federal Circuit's determination that it would not have been obvious to select compound '222 as a starting point represents the application of a rigid TSM rule that is inconsistent with *KSR*. Teva Pet. at 13-14; DRL Pet. at 13.

The clearest evidence that the Federal Circuit did not erect a rigid rule that precluded considering compound '222 is that the courts below both performed a full analysis under *Graham* analyzing whether, *starting with compound '222*, it would have been obvious to modify it to make olanzapine. App. 15a, 79a-80a ¶¶ 170-173, 222a-223a ¶¶ 63-64. The PTO, the district court, and the Federal Circuit all concluded that, *starting with compound '222*, olanzapine would not have been an obvious modification.

Similarly, DRL's complaint that the Federal Circuit limited the inquiry to only one specific lead compound, DRL Pet. at 12, is belied by the fact that the courts actually considered whether olanzapine would have been obvious from *two* lead compounds, compound '222 and flumezapine. App. 17a-18a, 80a-81a ¶¶ 174-177, 223a-224a ¶¶ 65-67.

To be sure, the courts below in this case concluded that one of ordinary skill would not have selected compound '222 as a lead compound. App. 14a-16a, 73a-76a ¶¶ 154-161, 220a-222a ¶¶ 60-62. But that was because the evidence showed that in the pharmaceutical arts, selecting a lead compound was a standard part of the discovery of new drugs. App. 16a. This was the very approach that a petitioner's expert testified would have been followed by a person of ordinary skill in this case. CA App. at A27165-66, *cited* DRL Pet. at 16. "[A] court can take account of the inferences and creative steps that a person of ordinary skill in

the art would employ." *KSR*, 127 S. Ct. at 1741. Thus, it makes sense to consider, as part of the analysis of obviousness of a pharmaceutical compound, whether a person of ordinary skill would have begun development with a particular prior art compound.

That "lead selection" and "lead following" is in fact the way pharmaceutical research is done is also clear from the pharmaceutical patent cases in which the obviousness issue was analyzed in this way. *See, e.g., Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1344 (Fed. Cir. 2000); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, No 06-1329, 2007 WL 1839698, at *4-*5 (Fed. Cir. June 28, 2007). Indeed, the Federal Circuit's recent, post-*KSR* decision in *Takeda* further confirms this. Applying *KSR*, the Federal Circuit affirmed the district court's finding of nonobviousness. In doing so, the Federal Circuit noted that the "district court made extensive findings of fact and conclusions of law as to the four *Graham* factors," *starting* with the finding that one of skill in the art would not have selected a prior art compound as a lead compound for modification. *Id.* at *4. This common sense consideration is completely consistent with *KSR* and the way pharmaceutical research is done.

> While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731.

> Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id. Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.*

Takeda, 2007 WL 1839698, at *5 (emphasis added).

KSR confirmed this Court's expansive and flexible approach to an evaluation of obviousness informed by common sense. Under the facts of this case, it is reasonable to take note of the unattractiveness of starting with compound '222. It simply would not have been obvious to modify compound '222 to make olanzapine if there were no reason to ever start with that compound.

Petitioners argue that it would have been obvious to modify compound '222 to make olanzapine by pointing to statements in the *Chakrabarti 1980a* publication and the '574 patent that the compounds may be used to treat schizophrenia. Teva Pet. at 4; DRL Pet. at 6, 16. This contention ignores the protracted history of failure in the prior art between 1975 and 1990. By 1990, the '574 patent, which had originally been filed in 1975, was in the same position as the many other patents that had prematurely described new compounds as antipsychotics, but later failed to live up to that promise. App. 82a ¶ 178. Indeed, even

petitioner's expert conceded that by 1990 no one would believe that all of the millions of compounds encompassed by the '574 patent disclosure would be effective antipsychotic drugs. CA App. A26571. Not surprisingly, therefore, the district court found, as a fact, that "[i]n 1990, a skilled artisan would not have reasonably expected, based on the data from the animal tests, that *any* of the compounds identified in *Chakrabarti 1980a* would be effective antipsychotics." App. 83a ¶ 180 (emphasis added). DRL's assertion that in 1990 it was believed that compound '222 exhibited "antipsychotic properties" and had "the same utility as olanzapine," DRL Pet. at 16, is erroneous and contradicted by the unchallenged factual findings of the district court.

If there was no reason to expect that those compounds would solve the problem, there was even less reason to specifically choose compound '222. According to the experimental data reported in *Chakrabarti 1980a,* compound '222 was considered "inactive," *see* App. 10a n.1, 57a ¶ 99, 60a ¶ 108, or at best did not meet the minimal criteria for further development as an atypical antipsychotic drug. App. 74a ¶ 156, 221a ¶ 61. This published experimental data showing the unpromising properties of compound '222 taught away from selecting that particular compound as a starting point. It reinforces the general teaching in the prior art that a neuroleptic substituent was required for activity.

Teva mischaracterizes the record and engages in impermissible hindsight by repeatedly asserting that it "would have been obvious to select ethyl olanzapine because it is the next adjacent homolog with the same disclosed activity." Teva Pet. at 9, 15. As shown *supra*, however, the pharmacological activity of compound '222 that was actually

disclosed in the prior art was weak and unpromising, and by 1990 one of skill in the art would not have believed the earlier predictions of antipsychotic activity for this genus of compounds. Petitioners' only reason to select compound '222 is that it is the adjacent homolog of what is known today to be a highly effective antipsychotic drug. App. 222a ¶ 63. This is precisely the kind of "argument[] reliant upon *ex post* reasoning" and "distortion caused by hindsight bias" that has no place in an analysis of obviousness. *KSR*, 127 S. Ct. at 1742.

2. It Would Not Have Been Obvious to Modify Compound '222 to Make Olanzapine

Petitioners repeatedly argue that it would have been obvious to modify compound '222 to make olanzapine because chemically the compounds are adjacent homologs. Teva Pet. at 9, 14-15, 19; DRL Pet. at 8, 20. The Federal Circuit and district court were well aware of this argument and rejected it. App. 12a, 15a, 44a ¶ 57, 46a ¶ 64, 73a ¶ 153, 222a-223a ¶¶ 63-64.

There is no *per se* rule that an adjacent homolog of a compound is necessarily obvious. The respective biological and pharmaceutical properties of the claimed compound and those in the prior art must be considered before a conclusion of obviousness can be reached. *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). Any suggestion that one chemical compound would have been obvious from a structurally similar chemical compound rests on an assumption that structurally similar compounds have similar properties. *See id.*; *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). When there is actual evidence that small changes in structure within

a family of related compounds do alter the resulting properties, the core assumption underlying the allegation of obviousness is refuted. Under the facts of this case there was such evidence. The properties of clozapine-like compounds in general were known to vary dramatically with small changes in structure. App. 65a-66a ¶ 127, 82a ¶ 178. Within this particular class of molecules, flumezapine and ethyl-flumezapine were both unexpectedly toxic and each in a different way, App. 37a-38a ¶¶ 33-38, and a dramatic unexpected difference existed in the effects on cholesterol between olanzapine and compound '222. App. 93a ¶ 209, 233a-234a ¶¶ 101-102. These unexpected results, as well as evidence that the art taught away from compounds lacking neuroleptic substituents and experimental evidence of the inadequate biological activity of compound '222, prove that olanzapine would not have been obvious from its adjacent homolog.

Petitioners argue that the prior art provided motivation to modify compound '222 to make olanzapine. In particular, petitioners argue that *Chakrabarti 1980* taught the desirability of substituting a short alkyl group such as methyl, ethyl, or isopropyl at the 2-position because it seemed to increase the central nervous system activity. Teva Pet. at 4, 16; DRL Pet. at 5. However, the district court considered that argument, but found that this observation applied to only a specific series of *fluorinated* compounds for which data showing this effect was presented. App. 68a-69a ¶ 139. (Olanzapine and compound '222 are not fluorinated.) The court concluded that:

> the paragraph in *Chakrabarti 1980a* in which this preferred substituent is revealed states a preference for short alkyl groups in the context of a fluorinated series of compounds;

> thus the article does not generally provide motivation or guidance relating to the effect of such substitution on fundamentally different unfluorinated molecules [like compound '222].

App. 80a ¶ 173. Similarly, DRL points to publications by Lilly in 1982 and 1989 to support its argument that a short alkyl substitution enhanced activity, allegedly providing motivation to make olanzapine from compound '222. DRL Pet. at 5. DRL fails to acknowledge that the district court specifically considered those publications and found that they were at best merely cumulative to information in *Chakrabarti 1980a*, App. 198a-199a ¶¶ 537-539, and provided further evidence that statements regarding short alkyl chain substituents were relevant to only fluorinated compounds and not to the fundamentally different non-halogenated compounds. App. 197a-198a ¶¶ 534-536. Thus, not only did the art teach away from making any modification of compound '222 that did not provide a neuroleptic substituent, but it also provided no reason to make the particular modification (substituting methyl for ethyl) that petitioners suggest. *Id.*, App. 79a ¶ 170, 80a ¶ 173.

DRL turns *KSR* on its head by arguing that the importance the Federal Circuit placed on the prior art's teaching away from making olanzapine amounts to the sort of rigid motivation test rejected in *KSR*. DRL Pet. at 13. *KSR* rejected focusing narrowly on whether the prior art explicitly provided motivation to combine or modify, when factors such as common sense and the availability of a few predictable solutions provided that motivation. *KSR*, 127 S. Ct. at 1742. But it is an entirely different situation when the prior art actually teaches *not* to make the invention, or to

make combinations or modifications *different* from the invention. Proceeding against the conventional wisdom and making an invention that persons of ordinary skill would not have expected to succeed are quintessentially what would *not* have been obvious to a person of ordinary skill. The importance of teaching away, and its distinctness from an impermissibly rigid TSM test, was recognized in *KSR* and in prior precedents of this court. *KSR*, 127 S. Ct. at 1740; *Adams*, 383 U.S. at 52.

DRL's argument that the prior art's teaching away from molecules that lacked a neuroleptic substituent was "litigation-inspired" is entirely devoid of merit. DRL Pet. at 13. The district court found that this was the state of the art based on extensive documentary and testimonial evidence. App. 14a-16a, 79a ¶ 170, 81a ¶ 176, 221a ¶ 61. Indeed, DRL's own expert conceded the point at trial. CA App. 27241-42.

3. The Federal Circuit Did Not Impose Requirements That Only "Preferred" Compounds or That Only "Preferred" Modifications Can Be Considered

Grasping for rigid and formalistic rules in the Federal Circuit's decision that would be inconsistent with *KSR*, petitioners pose two related arguments. First, they allege that the Federal Circuit required that only a compound that is described as "preferred" can be the starting point of an obviousness analysis. Teva Pet. at 14-15; DRL Pet. at 14. Second, they contend that the Federal Circuit forbade modification of a prior art compound to arrive at the patented compound unless the type of modification is described as

"preferred." Teva Pet. at 14-15; DRL Pet. at 14. There are simply no such rules in the decision below. As noted above, far from being forbidden by a rigid rule, the particular non-preferred solutions starting with compound '222 that petitioners advocate based on hindsight were actually considered and were rejected on the merits. App. 15a, 79a-80a ¶¶ 170-173, 222a-223a ¶¶ 63-64.

Teva admits that "it may have been obvious to select a halogenated compound because those compounds are described in the prior art as 'preferred,'" but argues that "it *also* would have been obvious to select [compound '222] because it was a next adjacent homolog with the same disclosed activity." Teva Pet. at 15. Teva characterizes this as one of the "finite number of identified, predictable solutions" that "a person of ordinary skill [would have had] good reason to pursue." *Id.* The argument fails at the outset because, as noted above, under the facts of this case there were not a finite number of identified, predictable solutions. It is only hindsight knowledge of the invention that identifies compound '222 as the adjacent homolog of the long-sought successful compound olanzapine. Moreover, this class of literally millions of molecules was highly unpredictable and there would have been no reasonable expectation of success. App. 15a, 67a ¶ 132, 82a-84a ¶¶ 178-182.

Furthermore, petitioners mischaracterize what a patent or publication teaches when it states that a type of compound or a type of modification is "preferred." Such a statement of preference not only provides a suggestion to use the preferred compound or modification, it can also teach away from using other non-preferred compounds or modifications. *See, e.g.*, *In re Baird*, 16 F.3d at 383 (statements of preference for other different compounds taught away from the claimed compounds). This is such a

case. The '574 patent disclosed millions of compounds. App. 67a ¶ 132. Its manifest preference for halogenated compounds not only taught that halogenated compounds should be tried, but also taught away from non-halogenated compounds like compound '222 and from modifying it to make another non-halogenated compound like olanzapine.

Furthermore, the courts below did not rely solely on the many prior art statements of "preference" for halogens as the basis for finding that the prior art taught away from non-halogenated compounds. Teaching away was also proven by testimony and prior art publications showing that neuroleptic substituents were considered to be necessary for antipsychotic activity. App. 6a, 14a-16a, 34a ¶ 24, 40a ¶ 44, 79a ¶ 170, 81a ¶ 176, 83a ¶ 179.

Petitioners' unsupported allegation that the Federal Circuit forbade consideration of modifications that were not "preferred" is equally flawed. Teva Pet. at 16; DRL Pet. at 14. Again, the alleged rigid requirement is nowhere to be found in the opinions below. Instead, the courts considered whether it would have been obvious to modify compound '222 to make olanzapine and found on the merits that it would not.

Petitioner's position about starting with non-preferred compounds and modifying them in non-preferred ways is tantamount to a contention that any modification that could have been abstractly conceived would have been obvious. The question under § 103(a) is not whether, with hindsight, it was abstractly possible to make the compound now known to be important by virtue of the claimed invention. The question here instead is whether it would have been obvious to a person having ordinary skill, knowing only what was in the prior art at the time the invention was made, that

olanzapine was a solution to the intractable problem of finding a safe atypical antipsychotic drug. Both of the courts below found that olanzapine simply would not have been obvious from the prior art.

4. Olanzapine Was Held to Be Nonobvious Because the Facts Contradicted the Petitioners' Theories

Petitioners did not fail to prove the obviousness of olanzapine because of legal error in the analyses of the lower courts. Rather, under the undisputed facts of this case, petitioners sought to prove an untenable factual proposition. Their argument was essentially that it would have been obvious for a person of ordinary skill (1) to select a compound for modification from a genus of compounds that one would not have expected, at the time of the invention, to be safe atypical antipsychotics, and (2) to then select for further development a particular compound, compound '222, that was rated as "inactive" or lacking a minimal score in an experimental test of potential antipsychotic activity, and that also lacked a neuroleptic substituent believed essential for activity. Petitioners' theory further required (3) that the person of ordinary skill would again ignore the teachings in the art that a neuroleptic substituent was essential for activity and instead modify compound '222 to obtain another compound that lacked a neuroleptic substituent. Common sense suggests that those choices would not have been obvious.

DRL's analysis, which is based on ignoring most of the prior art and looking at only four compounds selected through hindsight, is equally unreasonable. *See* DRL Pet. at 4, 17-18. Its argument reduces to a contention that given a

compound that caused a serious blood disease in animal toxicology tests (ethyl flumezapine), a compound that caused abnormal liver and muscle enzyme levels in humans (flumezapine), and a compound without a neuroleptic substituent that was predicted by experimental tests to have little or no antipsychotic activity (compound '222), the person of ordinary skill would have ignored other more promising options and instead would have modified compound '222 to make olanzapine because it neatly fills out a four-box square based on the hindsight selection of the other three compounds.

The weakness of petitioners' theories is evident even before one considers the overwhelming evidence of secondary indicia of nonobviousness, including unexpected results, long-felt but unsatisfied need, and failure of others. Rigid threshold rules had nothing to do with the petitioners' inability to prove obviousness.

C. DRL Ignores Most of the Evidence and the District Court's Undisputed Findings of Fact

DRL seeks here to retry the factual case that it lost below. Citing only disjointed fragments of the complete evidentiary record, DRL fills its brief with innuendo and factual allegations that were rejected by the trial court based on the totality of the evidence. The trial court's factual findings, however, were not challenged as clearly erroneous on appeal and were sustained.

For example, DRL insinuates that the Lilly toxicology study showing an unexpected effect of compound '222 on cholesterol was deficient because the elevation was only seen in four female dogs at a dose higher than the

proposed human dose. DRL Pet. at 6, 23. In fact, the propriety of the dose, sample size, different effect between the sexes, as well as all other potential criticisms of the study that petitioners advocated at trial, were intensively litigated, and the district court found as a matter of fact that the dose was appropriate, App. 105a-107a ¶¶ 238-241, the number of animals tested was adequate to prove statistical significance, App. 104a-105a ¶ 237, and sex-specific toxicities are known and important. App. 104a ¶ 236. The conclusion that elevation of cholesterol caused by compound '222 was unexpected, large, statistically significant, and medically important is not based solely on the Lilly study—it is buttressed by a sophisticated study performed for this litigation by the other petitioner that fully replicated the results of the Lilly study. App. at 91a-94a ¶¶ 205-211. There is no basis for DRL's suggestion, DRL Pet. at 23, that on remand this extensive and well-supported evidence of unexpected results would be any less probative of nonobviousness.[4] DRL's disparagement of the

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[4] Similarly, the district court was well aware of other factors that DRL insinuates undermine the nonobviousness of olanzapine. The court knew about the drug risperidone (DRL Pet. at 22; App. 227a ¶¶ 77-80, 230a ¶ 93), the circumstances under which the inventors conceived of olanzapine (DRL Pet. at 18-19; App. 39a-40a ¶¶ 40-43; *see* 35 U.S.C. § 103(a) ("Patentability shall not be negatived by the manner in which the invention was made.")), experimental parameters where the effects of olanzapine and compound '222 were not different (DRL Pet. at 21; App. 48a-50a ¶¶ 74-77), and publications by inventor Chakrabarti in 1982 and 1989 (DRL Pet. at 5; App. 197a-199a, ¶¶ 533-540). The district court weighed all of the evidence on these

nonobviousness of olanzapine should be disregarded as contrary to the factual findings of the district court and irrelevant to the issues upon which certiorari is being sought.

This Court has recognized the importance of deference to factual findings of a district court under Fed. R. Civ. P. 52(a), especially "where the evidence is largely the testimony of experts . . . ." *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 336 U.S. 271, 274-275 (1949), *aff'd on reh'g*, 339 U.S. 605 (1950). In the context of a patent case, the Court said that it "cannot undertake to review concurrent findings of fact by two courts below in the absence of a very obvious and exceptional showing of error." *Id.* at 275. DRL simply ignores the many adverse findings of fact and fails to show "obvious and exceptional error." *KSR* provides no basis for revisiting factual determinations that were fully litigated and never challenged on appeal as clearly erroneous.

D. GVR Is Unnecessary and Would Be a Futile Exercise

The decision that olanzapine would not have been obvious from compound '222 was not reached by application of rigid motivation tests, but rather arises from the application of well established legal principles to the unique facts of this case. As shown above, these include unchallenged evidence that (1) the prior art taught away from modifying the prior art compounds to obtain olanzapine, (2) the effects of modifications of this class of compounds were unpredictable so that there would have been no reasonable

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questions when determining that olanzapine would not have been obvious.

expectation of success, (3) olanzapine showed a significant unexpected benefit in a toxicology study, (4) there was a long-felt but unsatisfied need for a safe atypical antipsychotic, and (5) others tried but failed to solve the problem. Nonobviousness based on these facts is fully consistent with *Graham*, *Adams*, and *KSR* and was independent of the alleged errors in assessing "motivation" asserted by petitioners.

Petitioners' burden for overcoming this powerful evidence of nonobviousness was to come forward with clear and convincing evidence to the contrary, 35 U.S.C. § 282; *Takeda*, 2007 WL 1839698, at *3, and this they could not do based on the record below. *KSR* has not changed the legal basis for the holding of nonobviousness in this case. There is therefore no "reasonable probability that the decision below rests upon a premise that the lower court would reject if given the opportunity for further consideration," nor does it appear "that such a redetermination may determine the ultimate outcome of the litigation." *Lawrence v. Chater*, 516 U.S. 163, 167 (1996). GVR would be futile and a waste of judicial resources.

IV. CONCLUSION

For the foregoing reasons, the petitions of Teva and DRL should be denied.

Respectfully submitted,

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